UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 2 1990

008052

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SUBJECT: (U-^{14}C)-Phenyl CGA 64250: Absorption, Distribution, Metabolism and Excretion in the Rat

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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THRU: K. Clark Swentzel, Section Head
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MRID NO.: 413267-01 EPA REC. NO.: 257903 ID No.: 100-617

HED PROJECT NO.: 0-0477 CASWELL #: 323EE

REGISTRANT: Ciba-Geigy Corporation. P.O. Box 18300, Greensboro, NC

ACTION REQUESTED: To review a study entitled: (U-14C)-Phenyl CGA 64250: Absorption, Distribution, Metabolism and Excretion in the Rat

CONCLUSIONS:

This study investigated the absorption, distribution, metabolism and elimination of (^{14}C)-CGA 64250 following oral and intravenous administration to the rat. Dosage levels were 0.5 mg/kg for the low and 50.0 mg/kg for the high dose.

Administration of 0.5 mg/kg of radiolabelled CGA 64250 to rats by oral and intravenous routes resulted in similar patterns of elimination, possibly as a result of biliary excretion. Unmetabolized parent compound in the urine was observed in those animals which received the compound intravenously. Renal elimination data suggest that between 35-50% of the oral dose was absorbed. Only slight differences in the routes of excretion and in the pattern of metabolites were observed between the male and female rats in each group. Distribution and pattern of residual radioactivity were not affected by non-radiolabelled CGA 64250 pre-treatment.

After administration of 50 mg/kg radiolabelled CGA 64250, the residual radioactivity concentrations in the tissues, expressed as percent of the administered dose, were similar to the low dose group.

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Almost all administered radioactivity was recovered within 48 hours post dose in all groups. No detectable radioactivity was expired as $^{14}CO_2$.

Examination of the pooled urine and fecal extracts indicated that radiolabelled CGA 64250 was extensively metabolized into 24 and 47 different radiolabelled components respectively. Many of the metabolites were not identified in this study.

Within each sample type, the pattern of metabolites varied according to sex and dose group. Regardless of the route or the dose level, radiolabelled CGA 64250 was extensively degraded with metabolism possibly proceeding through side chain oxidation giving the hydroxylated propyl derivative or replacement of the propyl group by carboxylic acid. There is some evidence that the alkyl side chain attached to the dioxolane ring in CGA 64250 was attacked with the possible loss of the dioxolane ring itself. This finding is consistent with previously reviewed metabolism studies of radiolabelled CGA 64250 (July 18, 1979 and May 20, 1986) submitted by Ciba Geigy to this Agency.

RECOMMENDATIONS:

The present study is classified as core-supplementary and cannot be upgraded to core minimum because many of the metabolites representing a significant part of the original label were not identified.

CLASSIFICATION: Core-supplementary.

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Reviewed by : David S. Liem, Ph.D. David Liem 7/27/90
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DATA EVALUATION REPORT

STUDY TYPE: Metabolism in Rat GUIDELINE: 85-1

HED PROJECT NO.: 0-0477 MRID NO.: 413267-01 CASWELL #: 323EE

EPA REC. NO.: 257903 ID No.: 100-617

TEST MATERIAL: CGA 64250 SYNONYMS: Tilt; Propiconazole

SPECIES: Sprague Dawley rats STRAIN: Crl:CD(SD)BR

STUDY NUMBER: Hazelton UK # 380/105

SPONSOR: Ciba-Geigy Corporation. P.O. Box 18300, Greensboro, NC

TESTING FACILITY: Hazelton UK, Otley Rd., Harrogate, North Yorkshire, England HG3 1PY

TITLE OF REPORT: (U-14C)-Phenyl CGA 64250: Absorption, Distribution, Metabolism and Excretion in the Rat

AUTHOR: D.G. Cresswell, B.Sc., Ph.D.

REPORT ISSUED: June 2, 1989

CONCLUSIONS:

This study investigated the absorption, distribution, metabolism and elimination of (^{14}C)-CGA 64250 following oral and intravenous administration to the rat. Dosage levels were 0.5 mg/kg for the low and 50.0 mg/kg for the high dose.

Administration of 0.5 mg/kg of radiolabelled CGA 64250 to rats by oral and intravenous routes resulted in similar patterns of elimination, possibly as a result of biliary excretion. Unmetabolized parent compound in the urine was observed in those animals which received the compound intravenously. Renal elimination data suggest that between 35-50% of the oral dose was absorbed. Only slight differences in the routes of excretion and in the pattern of metabolites were observed between the male and female rats in each group. Distribution and pattern of residual radioactivity were not affected by non-radiolabelled CGA 64250 pre-treatment.

After administration of 50 mg/kg radiolabelled CGA 64250, most of this compound was eliminated within 48 hours and the residual radioactivity concentrations in the tissues, expressed as percent of the administered dose, were similar to the low dose group.

Almost all administered radioactivity was recovered within 48 hours post dose in all groups. No detectable radioactivity was expired as $^{14}CO_2$.

Examination of the pooled urine and fecal extracts indicated that radiolabelled CGA 64250 was extensively metabolized into 24 and 47 different radiolabelled components respectively. The latter may reflect a difference in assay sensitivity as well as a dose level effect.

Within each sample type, the pattern of metabolites varied according to sex and dose group. Regardless of the route or the dose level, radiolabelled CGA 64250 was extensively degraded with metabolism possibly proceeding through side chain oxidation giving the hydroxylated propyl derivative or replacement of the propyl group by carboxylic acid. There is some evidence that the alkyl side chain attached to the dioxolane ring in CGA 64250 was attacked with the possible loss of the dioxolane ring itself.

Because many of the metabolites representing a significant part of the original label were not identified, the study cannot be upgraded to core minimum.

Classification: Core-supplementary.

Compliance Statements:

- Quality Assurance Statement was signed and dated by Quality Assurance Unit
- FIFRA GLP Compliance Statement was signed and dated

Study Title: (U-^{14}C)-Phenyl CGA 64250: Absorption, Distribution, Metabolism and Excretion in the Rat

Objective of Study:

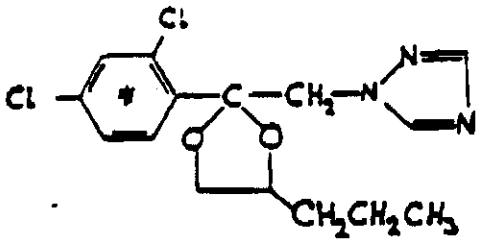
The objectives of the study were to examine the absorption, distribution, bioaccumulation/bioretention and elimination of CGA 64250 and/or its metabolites following administration of radiolabelled CGA 64250 to the rat at two dose levels. The number, nature and quantity of radiolabelled metabolites excreted in urine and feces were also investigated.

Testing Period: April 1987 - February 1988

Test Material:

The radiolabelled compound had a specific radioactivity of 38.9 Ci/mg and a radiochemical purity of >99%. The radiolabelled and non-radiolabelled CGA 64-250, and seven analytical standards were supplied by Ciba Geigy, Basel, Switzerland. Radiochemical purity was determined to be in excess of 99% by thin layer chromatography using ethyl acetate as a solvent. Test articles were stored in the dark at 0-4°C, and radiolabelled CGA 64250 was stored at -20°C.

The (U-^{14}C)-phenyl CGA 64250 used in this study had the following structure:



* Uniformly labelled with carbon-14

The identity and the structure of the other seven analytical standards, i.e. CGA 21496, CGA 217495, CGA 118245, CGA 118244, CGA 91304, CGA 91305, and CGA 177291 are presented in Appendix D.

Test Animals:

A total of fifty Sprague-Dawley rats (Crl:CD(SD)BR strain), 23 males and 27 females (nulliparous and non-pregnant), weighing 142-198 g and between 6 to 10 weeks old on arrival were used. Rats were obtained from Charles River (UK) Ltd., Manston Rd., Margate Kent. Rats were held in an experimental room for about 1 to 2 weeks prior to study initiation. Commercial pellet diet, "SQC Rat and Rat Maintenance Diet No. 1, Expanded", obtained from Special Diets Services, Stepfield, Witham, Essex, CM8 3AB, was provided to all rats ad libitum, except for at least 16 hours (overnight) prior to dosing of radiolabelled test article. Water was provided ad libitum throughout the study.

Prior to dosing, animals were housed up to five per cage in a controlled environment; temperature between 16° and 27°C, relative humidity 52-82%, and a 12 hours light-dark cycle.

Study Design and Test Procedures:

a. Route of Administration

The test article was administered by oral gavage, since this oral route is the possible route of human exposure. The test article was also administered intravenously to determined what proportion of an oral dose was absorbed.

b. Dose Levels

Two dose levels were used, a high dose of 50 mg/kg body weight which is known to produce some toxic and pharmacologic effects and a low dose of 0.5 mg/kg body weight which produced no such effects.

c Dosing Procedures

Radiolabelled CGA 64250 was administered to four groups of rats, each comprised of at least five rats per sex. In order to take into account of unforeseen complications, four extra (exact number assigned to each group was not indicated) rats were dosed with radiolabelled test article in groups A and C, and six extra (3 males and 3 females) rats were dosed with non-radiolabelled test article in group C. Data from only five rats of each sex per dose group were used in the analyses. Groupings and dosing procedures are as follows:

Groups	# Rats M/F	Test Article (CGA 64,250)	Dose Level	Dosing Methods
A	5/5@	Radiolabelled	0.5 mg/kg	Single Intravenous
B	5/5	Radiolabelled	0.5 mg/kg	Single Oral Dose
C	8/8*	Non-Radio-labelled	0.5 mg/kg	Daily Single Oral Dose for 14 Days and
	5/5@	Radiolabelled	0.5 mg/kg	Single Oral Dose, 24 Hours After Last Dose
D	5/5	Radiolabelled	50.0 mg/kg	Single Oral Dose

* Six (3 males and 3 females) additional rats were added for the 14-day non-radiolabelled daily single oral dose administration.
@ A total of four additional rats were treated with radiolabelled dose (specific assignment not specified).

d. Dose Formulation

Radiolabelled CGA 64250 was administered orally as a solution mixed in ethanol, polyethylene glycol 200, and water (2:4:4, by volume) and intravenously as a solution in physiological saline.

The stability of radiolabelled compound for both the low and high dose formulations under the proposed dosing conditions were measured, and showed no significant degradation or change in the concentration over 4 hr and 20 hr (I.V. formulation), and 44 days (oral formulation).

e. Collection of Samples

1. Excretion Studies

After radiolabelled dose administration, the rats were placed in individual all-glass metabolism cages suitable for separate collection of urine, feces and expired air samples. Urine and feces samples were made at the following intervals: 0-6, 6-12, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr. Expired air samples were made at 0-6, 6-12, and 12-24 hr intervals. For group C urine and feces collections were terminated at 120 hr.

2. Tissue Distribution Study

At 168 hr post-dose for groups A, B, and D, and at 120 hr post-dose for group C, rats were anesthesized with diethyl ether, and then exsanguinated. The following tissues were collected and assayed for radioactivity: blood, brain, heart, liver, lung, spleen, adrenals, kidney, uterus, gonads, bone, bone marrow, skeletal muscle, fat, and residual carcass.

3. Metabolism Study

Urine samples and methanolic fecal extracts from each rat containing the highest concentrations of radioactivity were pooled by sample type, sex and dose group. The pooled samples were tested for evidence of metabolism by two dimensional TLC. Following chromatography, the radiolabelled metabolites were located by apposition autoradiography. Adsorbent containing radioactivity was removed from the plate and transferred to an individual liquid scintillation vial, and after water was added, the radioactivity content of each vial was measured by liquid scintillation counting.

4. Data Analysis and Determination of Radioactivity

Data analysis and radioactivity determination of biological samples are appended as Appendix A.

RESULTS AND DISCUSSION:

As noted earlier, a total of ten extra rats were dosed in groups A and C. Six additional rats (3 rats of each sex) were dosed with non-radiolabelled test article daily for 14 days in group C. It was not clearly stated in the text, how the other four extra rats were assigned into groups A and C. On p. 25, the investigator noted that "Due to low recoveries from 2 animals in group A and one in group C, four additional animals were also treated with ^{14}C-CGA 64250", but on p. 23, however, it was noted that "Because of low recoveries of radioactivity two additional animals to those reported were dosed in dose groups A and C". These contradictory statements and what criteria the investigator used to exclude certain data from the analyses are of concern.

Excretion Studies

Recovery of mean percent radioactivity from rats (5 males and 5 females per group) at 168 hours following treatment can be summarized as follows:

Mean Percent Recovery of Radioactivity
(5 males and 5 females per group)

	Group A M / F	Group B M / F	Group C M / F	Group D M / F
Urine	42.9/46.3	38.7/43.8	40.6/45.6	39.2/48.7
Feces (Total)	42.0/39.0	50.2/37.0	48.4/39.9	47.9/37.0
o Extract	19.6/19.0	25.0/18.8	19.8/18.1	24.4/20.5
o Residue	22.4/20.0	25.2/19.1	28.6/21.8	23.5/16.5
Cage Washing	4.9/8.5	7.0/12.5	6.5/9.8	5.6/8.4
Cage Debris	<0.1/0.1	ND/ND	ND/<0.1	0.7/<0.1
Expired Air	ND/ND	ND/ND	ND/ND	ND/ND
Tissues	0.1/0.1	0.1/0.1	0.1/0.1	0.1/<0.1
Carcass	ND/ND	ND/ND	ND/0.1	ND/0.2
Total Recovery				
0 - 48 hrs	87.7/90.9	95.3/93.8	93.5/94.0	88.7/91.8
0 - 168 hrs	89.7/93.9	96.0/94.3	95.6/96.4	93.4/94.3

M = Male; F= Female; ND = Not Detected

As seen from the above table, following a single oral dose the radioactivity excreted via the urine was lower than that of the feces in the low and high dose groups (group B and D). A similar pattern was exhibited for group C (14-day pretreatment followed

with a single radiolabelled oral dose). In all treatment groups, renal elimination was slightly greater in the females than in the males, but the reverse was true for the fecal elimination value.

The cage washing radioactivity value was higher for the females as compared to the males in all treated groups. In the tissues and in the carcass only a trace of radioactivity was recovered or was not detected at all. No measurable radioactivity was expired as $^{14}CO_2$.

Most of dose administered was eliminated within 48 hr post-dosing in all treatment groups (between 87.7-95.3%), with little additional radioactivity recovered in the 48-168 hr samples.

Tissue Distribution Studies

Mean concentrations (g equivalent of (^{14}C)-CGA 64250/g) and mean recovery (% of administered dose/tissue) of radioactivity from the tissues of rats following administration of radiolabelled CGA 64250, are presented in the attached Appendices B and C.

As seen in Appendix B, the mean tissue concentrations of radioactivity were generally low or below the limits of detection.

Except for group B males and group C females, in general the distribution of radioactivity in the tissues was similar in all treated groups. In group B males, the distribution of detected radioactivity was restricted to fat, kidney, liver and muscle tissues. In the group C females, the distribution of radioactivity was more widespread and it was detected in almost all rats. However, radioactivity was only detected in one rat each in the bone marrow and bone tissues. In the intravenous dose group A, radioactivity was generally more widely distributed between the tissues as compared to the single oral low dose group B.

The highest levels of radioactivity were detected in the kidney and liver in most rats in all treated groups. In the high dose group D, the absolute radioactivity concentration values in tissues were higher than those of group B (low dose). However, in terms of percent of dose administered, the radioactivity levels in the high dose were similar to those of the low dose group.

Metabolism Studies

Urine and fecal extracts containing highest concentrations of radioactivity were pooled by sex and dose group and these pooled samples were tested for evidence of metabolism by two-dimensional thin layer chromatography (TLC).

The administered radiolabelled CGA 64250 was extensively metabolized into 24 different radiolabelled components in the pooled urine.

Percentages of components recovered in the pooled urine detected by the two dimensional TLC that chromatographically corresponded to the parent compound, (^{14}C)-CGA 64250, or to any of the known standards, the number of unidentified and the total detected components, and total mean radioactivity recovery (% of total dose) in each dose group are summarized as follows:

Percentages of Urinary Radioactivity Recovered

Parent/Standard/ Unknown/Total	Group A M / F	Group B M / F	Group C M / F	Group D M / F
CGA 64250	27.1/29.9	- / -	- / -	- / -
CGA 188245	61.8/ 2.4	19.2/14.4	- / -	- /49.3
CGA 217495	8.9/58.3	- / -	3.5/ -	- / -
CGA 91304	2.3/ -	11.5/14.9	28.6/ -	- / -
CGA 118244	- /3.6	- / -	3.6/ -	- / -
CGA 217496	- / -	- / -	- / -	- / -
Total Mean Radioactivity Recovery (% Total Dose)	42.9/46.3	38.7/43.8	40.6/45.6	39.2/48.7
No. of Components				
o Detected	4 / 5	4 / 4	6 / 3	8 / 7
o Identified	4 / 4	2 / 2	3 / -	- / 1
o Unidentified	- / 1	2 / 2	3 / 3	8 / 6

As seen from the above table, in the urine, the radiolabelled parent compound was only detected in group A (I.V. administration) males (27.1%) and females (29.9%), and none was detected when administered orally. Apparently absorbed radiolabelled CGA 64250 was completely metabolized when given by oral route. The pattern of metabolites detected varied according to sex and dose group. In dose group A, most of the metabolites (5 of 6) were identified, and corresponded chromatographically to the parent compound or to the other known standards. In the dose group C, only three out of the six metabolites corresponded chromatographically to the known standards. In the high dose group D, only one metabolite (49.3%) in the female corresponded to the known standard CGA 118245; the remaining eight components did not correspond to any of the other standards. Regardless of the route of administration or dose level, urine contained many polar components as indicated by the low R_f values in the ethyl acetate : propan-2-ol solvent system. It is of particular concern that many metabolites were not identified.

Percentages of components in the pooled fecal extracts detected by the two dimensional TLC that chromatographically corresponded to the parent compound, (^{14}C)-CGA 64250, or to any of the known standards, the number of unidentified and the total detected components, and total mean radioactivity recobery (% of total dose) in each dose group can be summarized as follows:

Percentages of Fecal Extract Radioactivity Recovered

Parent/Standard/ Unknown/Total	Group A M / F	Group B M / F	Group C M / F	Group D M / F
CGA 64250	- / -	6.8/13.9	14.6/13.6	5.7/17.6
CGA 91305	7.3/5.1	8.2/7.6	8.0/ -	- /7.6
CGA 188245	10.4/8.6	8.1/ -	6.0/ -	- /10.9
CGA 177291	- / -	- / -	- / -	- /0.5
Total Mean Radioactivity Recovery (% Total Dose)	42.0/39.0	50.2/37.0	48.4/39.9	47.9/37.0
No. of Components				
o Detected	12 / 9	13 / 6	13 / 7	29 / 24
o Identified	2 / 2	3 / 2	3 / 1	1 / 3
o Unidentified	10 / 7	10 / 4	10 / 6	28 / 21

The radiolabelled CGA 64250 was extensively metabolized into 47 different radiolabelled components in the pooled fecal extract, most of which were very polar, as indicated by the low R_f values in the ethyl acetate : propan-2-ol solvent system.
Only three components, the parent compound and two other metabolites that corresponded to two known standards (CGA 91035 and CGA 188245) were detected.
As seen from the table above, the overall pattern of metabolites detected in the feces was slightly different than in the urine. Percentages of detected metabolites were slightly varied according to sex and dose group. No parent compound was detected in the feces of group A rats, but this parent compound was detected in both sexes of groups B (6.8/13.9%), C (14.6/13.6%), and D (5.7/17.6%). The parent compound was not present in the feces of group A (intravenous dose) or in the urine of orally treated rats, suggesting that orally-administered radiolabelled CGA 64250 was not totally absorbed by the rat.

The two known components that corresponded to CGA 91035 and CGA 118245 were present in every dose group, however, they were not detected in the group C females or group D males. The metabolite that corresponded to CGA 188245 was not detected in group B females.

It is of particular concern that many of the metabolites were not identified.

CONCLUSIONS:

Administration of 0.5 mg/kg of radiolabelled CGA 64250 to rats by oral and intravenous routes resulted in similar pattern of elimination, possibly as a result of biliary excretion. Renal elimination data suggest that between 35-50% of the oral dose was absorbed. Only slight differences in the routes of excretion and in the pattern of metabolites were observed between the male and female rats in each group. Distribution and pattern of residual radioactivity were not affected by non-radiolabelled CGA 64250 pre-treatment.

Administration of 50 mg/kg radiolabelled CGA 64250 did not affect pattern of elimination, and most of the compound was eliminated within 48 hours. In this group, the residual radioactivity concentrations in tissues, expressed as percent of administered dose, were similar to the low dose groups.

Almost all administered radioactivity was recovered within 48 hours post dose in all groups. No detectable radioactivity was expired as $^{14}CO_2$.

Examination of the pooled urine and pooled fecal extracts indicated that radiolabelled CGA 64250 was extensively metabolized into 24 and 47 different components, respectively. Unmetabolized parent compound was present in the urine only in those rats which received the dose intravenously. However, these same rats did not have any unmetabolized parent compound in the feces, as did the groups which received the test material by oral gavage.

Within each sample type, the pattern of metabolites varied according to sex and dose group. Regardless of the route or the dose level, radiolabelled CGA 64250 was extensively degraded with metabolism possibly proceeding through side chain oxidation giving the hydroxylated propyl derivative or replacement of the propyl group by carboxylic acid. There is evidence that the alkyl side chain attached to the dioxolane ring in CGA 64250 was attacked with the possible loss of the dioxolane ring itself.

Because many of the metabolites representing a significant part of the original label were not identified, the study cannot be upgraded to core minimum.

Classification: Core-supplementary

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Page ___ is not included in this copy.

Pages 13 through 21 are not included in this copy.

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